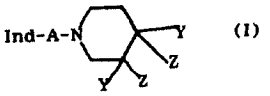
85-141748/24 B02 C02 MERE 25.11.83
MERCK PATENT GMBH *DE 3342-632-A
25.11.83-DE-342632 (05.06.85) A61k-31/44 C07d-401/06

N-Indolyl-alkyl-tetra:hydro-pyridine or piperidine(s) - with central nervous system, esp. dopamine stimulating, activity

BC(6-D1, 12-C4, 12-C6, 12-C10, 12-D1, 12-E2, 12-F5, 12-G1, 12-G4, 12-H5, 12-K3) 8 030

C85-061759 Indole derivs. of formula (I) and their physiologically acceptable acid addn. salts are new:



(I)

Ind = indol-3-yl substd. by CH_2OH or COW, and opt. also by 1 or 2 alkyl, alkoxy, OH, F, Cl or Br;
W = H, OH, alkoxy or amino (opt. substd. by 1 or 2 alkyl);
A = $(CH_2)_n$ or $CH_2S(O)_xCH_2CH_2$;
n = 2-5;
x = 0, 1 or 2;
both Y are H, or together form a bond;
one Z = Ar and the other is H;
Ar = phenyl (opt. substd. by 1 or 2 alkoxy and/or OH, or by one methylenedioxy) or 2- or 3-thienyl;
all alkyl have 1-4C.

USE

(I) have CNS, esp. dopamine-stimulating, activity, and also analgesic and blood-pressure reducing actions. They can be used in human or veterinary medicine and may be used as intermediates for other pharmaceuticals.

Typical applications are treatment of Parkinson's disease (esp.), extrapyramidal effects of neuroleptics, depression, psychoses, side effects of treatment of hypertension, acromegalia, hypogonadism, sec. amenorrhoea, premenstrual syndrome, unwanted lactation (and more generally as a prolactin inhibitor) and migraine, and they are also useful in geriatric medicine (in the same way as ergot alkaloids).

DOSE

The usual daily dose is 0.001-10 mg./kg.

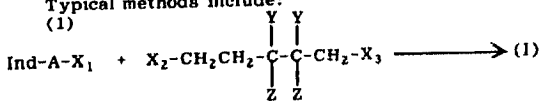
SPECIFICALLY CLAIMED

3-[4-(4-Ph-1,2,3,6-tetrahydropyridyl)butyl]indole-5-carboxylic acid and the corresp. amide.

PREPARATION

Typical methods include:

(1)

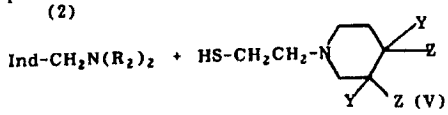


(I)

X_1 = X or NH_2;
each of X_2 and X_3 = X when X_1 = NH_2, otherwise they are together NH;
X = Cl, Br, I or opt. modified OH.

Reaction is at 0-150, pref. 20-30, °C., opt. in the presence of an acid acceptor.

(2)



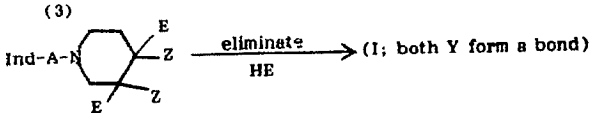
(V)

⟶ (I; A = $-CH_2S-CH_2CH_2-$)

R_2 = 1-4C alkyl or both together are $(CH_2)_4$, $(CH_2)_5$ or $(CH_2)_2O(CH_2)_2$.

Reaction is pref. at 60-150°C., esp. after conversion of (V) to a mercaptide.

(3)



(I; both Y form a bond)

One E = X, CN or NH_2 and the other is H.

Reaction is e.g. with a base when E = halo or by heating at 50-200°C. when E = CN.

EXAMPLE

A soln. of 28.4g. methyl 3-(4-chloro-2-thiabutyl)indole-3-carboxylate and 16g. 4-phenyl-1,2,3,6-tetrahydropyridine in 100 ml. acetonitrile was stirred for 12 hr. at 20°C. The mixt. was worked-up conventionally to give methyl 3-(4-(4-phenyl-1,2,3,6-tetrahydropyridyl)-2-thiabutyl)indole-5-carboxylate hydrochloride, m.pt. 202-203°C.
(52pp1251HDDwgNo0/0).